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PCT / IN 05 / 0 0 0 1 0

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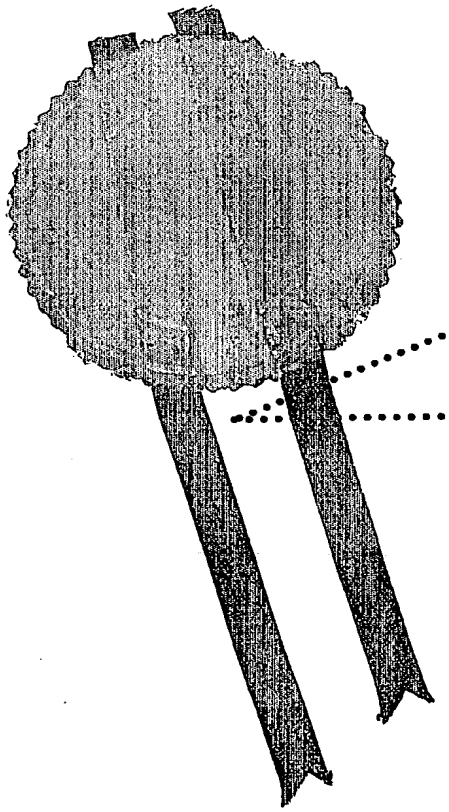
Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 09/01/2004 in respect of Patent Application No.22/MUM/2004 of **CADILA HEALTHCARE LIMITED**, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.



Dated this 23rd day of February 2005.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS

ORIGINAL

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT
(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, **CADILA HEALTHCARE LIMITED,** a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare –

(a) That we are in possession of an invention titled

'Novel Substituted Hydroxamic Acid Derivatives'

(b) That the Provisional Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that the true and first inventors for the said invention are ,

Braj Bhushan LOHRAY, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

Vidya Bhushan LOHRAY, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

Mukul R JAIN, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

Pravin S THOMBARE, an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: **NIL**

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;

M/s Subramaniam, Natraj & Associates
Attorneys-At-Law
E-556, Greater Kailash-II
New Delhi - 110 048, India.

Phone: +91 11 29215603, 29226012, 29216025
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22/mum/2004
9/1/2004

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- 9 JAN 2004

Received Rs. 3580/- on account of P.F.O. 9/1/04
Vide Entry No. 6271 in the Register of Patents, Bombay.

(7) Following declaration was given by the inventors

We, **Braj Bhushan LOHRAY, Vidya Bhushan LOHRAY, Mukul R JAIN, Pravin S THOMBARE** all Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India,

and the true and first inventors for this invention declare that the applicants herein as my assignees.

Braj Bhushan LOHRAY

Vidya Bhushan LOHRAY

Mukul R JAIN

Pravin S THOMBARE

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

(9) Following are the attachments with this application:
- (a) Provisional specification in triplicate
- (b) Statement and Undertaking on FORM 3 in duplicate
- (c) Power of Authority
- (d) Form 2 in triplicate
- (e) Power of Authority
- (f) Abstract

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No..... dated.....on .....Bank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 7th day of JANUARY, 2004.

The Controller of Patents
The Patent Office,
At Mumbai

for CADILA HEALTHCARE LIMITED
(Dr. B. B. Lohray, President, Zydus Research Centre)

Form 2

THE PATENTS ACT, 1970
(39 Of 1970)

PROVISIONAL SPECIFICATION
(Section 10; rule 13)

ORIGINAL

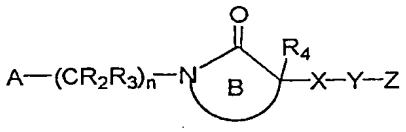
"Novel Substituted Hydroaxamic Derivatives"

We, **CADILA HEALTHCARE LIMITED**, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Road, Ahmedabad 308 015, Gujarat, India

The following specification describes the nature of the invention:

FIELD OF INVENTION

The present invention relates to novel compounds having MMP and TNF inhibitory activities, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel hydroxamic acids of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, use of these compounds in medicine and the intermediates involved in their preparation.



(I)

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutical compositions containing them.

The compounds of the present invention are useful as inhibitors of matrix-degrading metalloproteinases, reprolysin (also known as adamylsin) subfamilies and of TNF-alpha (tumor necrosis factor alpha) activity. The invention also describes a method of inhibiting TNF-alpha and matrix degrading metalloproteinase activity and a method of treating TNF-alpha and matrix metalloproteinase dependent diseases or conditions in mammals which are responsive to matrix metalloprotease and TNF-alpha inhibition, using such compounds of this invention or pharmaceutical compositions comprising such compounds of this invention.

BACKGROUND OF INVENTION

A number of enzymes effect the breakdown of structural proteins and many of them are structurally related to metalloproteases especially of the zinc metalloendopeptidases family. Matrix-degrading metalloproteinases (MMP) and reprolysin are examples of zinc metalloendopeptidases. Matrix-degrading metalloproteinases (MMP), such as gelatinase, stromelysin and collagenase, have been found to play an important role in the uncontrolled

breakdown of connective tissue, including proteoglycan and collagen, which leads to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone diseases (e.g. osteoporosis and Paget's disease), tumor metastasis or invasion, as well as HIV-infection.

The mammalian reprolysins are known as ADAMs (A Disintegrin And Metalloproteinase) [Wolfberg, et. al., J Cell Biol., 131, 275-78 (1985)] and they contain a disintegrin domain in addition to a metalloproteinase-like domain. Of the twenty-three different ADAMs identified, ADAM-17, also known as tumor necrosis factor-alpha converting enzyme (TACE) is the most well known. TACE is responsible for cleavage of cell bound tumor necrosis factor-alpha (TNF-α, also known as cachectin). TNF- α is recognized to be involved in many infectious and auto-immune diseases [W. Friers, *FEBS Letters*, 285, 199 (1991)]. Further, TNF- α has been shown to be the prime mediator of the inflammatory response seen in sepsis and septic shock. Two forms of TNF- α are known, a type II membrane protein having a relative molecular mass of 26 kD and a soluble 17 kD form, which is generated from the cell, bound protein by specific proteolytic cleavage. The 17 kD TNF-α is released by the cell and is associated with the deleterious effects of TNF-α. Another feature of this form of TNF-α is that it can act at sites remote from the site of synthesis. Compounds, which are inhibitors of TACE, prevent the formation of TNF-α and prevent the deleterious effects of the soluble factor.

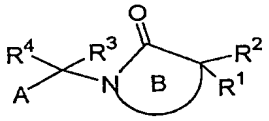
The compounds of the invention are useful in the treatment of but not limited to arthritis (including osteoarthritis and rheumatoid arthritis), inflammatory bowel disease, Crohn's disease, emphysema, malaria, acute respiratory distress syndrome, asthma, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, inflammation, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer and hematopoietic malignancies including leukemias and lymphomas), mycobacterial infection, meningitis, graft rejection, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, hyperoxic alveolar injury, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, abnormal wound healing, burns,

diabetes, tumor invasion tumor growth, tumor metastasis, corneal scarring, scleritis, AIDS, sepsis or septic shock.

Since excessive TNF production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may also have a particular advantage in diseases where both mechanisms are involved.

Compounds which inhibits TACE activities are described in WO0228846, WO0204416, WO0170673, WO0059285, WO0059874, WO0044710, WO9965867, WO 9958531, US 2003/0225054, US 6620823, US 6268379, US 6153757, US6057336, US6114361, EP1134215, EP1041072 which are all incorporated herein as reference.

US 6057336 describes MMP inhibitors of formula (A):



(A)

wherein

A is selected from –CONHOH, -CONHOR^5, -COR^5, -CO_2H, -CH_2CO_2H, -CO_2R^6, -N(OH)COR^5,- SH,-CH_2SH, -SO_2NHR^a, -$SN_2H_2R^a$, -$PO(OH)_2$, and -PO(OH)NHR^a;

ring B is a 4-8 membered cyclic amide containing from 0-3 additional heteroatoms selected from O, NR^a, and $S(O)_p$, 0-1 additional carbonyl groups and 0-1 double bonds;

R^1 is U-X-Y-Z-U^a-X^a-Y^a-Z^a;

U is absent or selected from: O, -NR^a, C(O), C(O)O, OC(O), CONR^a, NR^{a}C(O), OC(O)O, OC(O)NR^a, NR^{a}C(O)O, NR^{a}C(O)NR^a, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$;

X is absent or selected from $(C_{1\text{-}10})$alkylene, $(C_{2\text{-}10})$alkenylene, and $(C_{2\text{-}10})$ alkynylene;

Y is absent or selected from O, NR^a, $S(O)_p$, and C(O);

Z is absent or selected from a $(C_{3\text{-}13})$carbocyclic residue which may be substituted with 0-5 R^b and a 5-14 membered heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

U^a is absent or is selected from: O, NR^a, C(O), C(O)O, OC(O), CONR^a, NR^{a}C(O), OC(O)O, OC(O)NR^a, NR^{a}C(O)O, NR^{a}C(O)NR^a, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$; X^a is absent or selected from $(C_{1\text{-}10})$alkylene, $(C_{2\text{-}10})$alkenylene, and $(C_{2\text{-}}$

$_{10}$)alkynylene; Y^a is absent or selected from O, NR^a, $S(O)_p$, and C(O); Z^a is absent or selected from a (C_{3-13}) carbocyclic residue which may be substituted with 0-5 R^c and a 5-14 membered heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c; R^b, at each occurrence, is independently selected from (C_{1-6})alkyl, OR^a, Cl, F, Br, I, =O, CN, NO2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3 and CF_2CF_3;

R^c at each occurrence, is independently selected from (C_{1-6})alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3 and CF_2CF_3, -CH(=NOH), -(=NOH)CH_3, $(CRR')_sO(CRR')_{s'}R^d$, $(CRR')_sS(O)_p(CRR')_{s'}R^d$, $(CRR')_sNR^a(CRR')_{s'}R^d$, phenyl, and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O and S;

R^5 at each occurrence, is selected from (C_{1-10})alkyl substituted with 0-2 R^b, and (C_{1-8}) alkyl substituted with 0-2 R^d; R^d, at each occurrence is independently selected from phenyl substituted with 0-3 R^b, biphenyl substituted with 0-2 R^b.

US 2003/0225054 also discloses TACE inhibitors having a similar general formula as US 6057336. In this application, R^c denotes a (C_{1-6})alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3 and CF_2CF_3, -CH(=NOH), -(=NOH)CH_3, $(CRR')_sO(CRR')_{s'}R^d$, $(CRR')_sS(O)_p(CRR')_{s'}R^d$, $(CRR')_sNR^a(CRR')_{s'}R^d$, phenyl, $(CH_2)_r$-C_{3-6} membered carbocyle and a $(CH_2)_r$-5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O and S.

SUMMARY OF INVENTION

The present invention relates to novel compounds of formula (I) having MMP and TNF inhibitory activities. Such compounds are useful in the treatment of diseases such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone diseases (e.g. osteoporosis and Paget's disease), tumor metastasis or invasion.

OBJECTIVES OF THE INVENTION

The main objective of the present invention is to provide novel substituted hydroxamic acid derivatives represented by the general formula (I), their derivatives, their analogs, their

tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutical compositions containing them or their mixtures thereof.

Another objective of the present invention is to provide novel substituted hydroxamic acid derivatives represented by the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and pharmaceutical compositions containing them or their mixtures thereof having enhanced activities, without toxic effects or with reduced toxic effect.

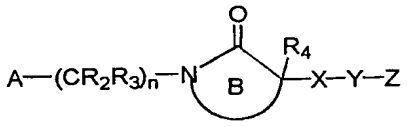
Yet another objective of this invention is to provide a process for the preparation of novel substituted hydroxamic acid derivatives represented by the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates.

Still another objective of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

A further objective of the present invention is to provide process for preparation of intermediates involved in the process.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I),



(I)

their derivatives, their analogs, there tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, wherein

A at each occurrence is independently selected from $-COR_1$, $-CO_2H$, $-CH_2CO_2H$, -CONHOH, $-CONHOR_1$, $-N(OH)COR_1$, $-C(=NOR_1)NHR_1$, -SH, $-CH_2SH$, $-SO_2NHR_1$, $-S(=NH)_2R_1$, $PO(OH)_2$ and $PO(OH)NHR_1$.

R_1 represents hydrogen, substituted or unsubstituted groups selected from linear or branched (C_1-C_8)alkyl, (C_3-C_7)cycloalkyl, acyl, aryl, aralkyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, heteroarylaminocarbonyl, heteroaralkylaminocarbonyl, or heterocyclylaminocarbonyl;

R_2 and R_3 may be same or different and independently represent hydrogen, halogen, substituted or unsubstituted groups selected from linear or branched (C_1-C_8)alkyl, (C_3-C_7)cycloalkyl, acyl, groups, substituted or unsubstituted groups selected from (C_3-C_7)cycloalkyl, aryl, aralkyl, heteroaryl, heterocycle groups, or R_2 and R_3 together represent =O;

B represents a 4-8 membered saturated or unsaturated cyclic amide, which may optionally contain from 0-3 additional heteroatoms selected from O, N, and S, and may optionally be substituted.

X and Z may be same or different and selected from (C_3-C_{13}) carbocyclic residue or a 5-14 membered heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, or S,

with the proviso that when

i) X represents substituted (C_3-C_{13})carbocyclic residue or a 5-14 membered substituted heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, or S, when Z is substituted with substituted or unsubstituted groups selected from alkene, alkyne or $(CH_2)_r$-3-4 membered heterocycle comprising carbon atoms and 1 heteroatom selected from the group consisting N, O and S, or substituted groups selected from $(CH_2)_r$-(C_3-$_6$)cycloalkyl, $(CH_2)_r$-cycloalkene, $(CH_2)_r$-phenyl, alkyl or $(CH_2)_r$-3-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting N, O and S;

ii) Z represents substituted (C_3-C_{13})carbocyclic residue or a 5-14 membered substituted heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, and S, when X is substituted with substituted or unsubstituted groups selected from $(CH_2)_r$-phenyl, $(CH_2)_r$-cycloalkyl, $(CH_2)_r$-cycloalkene, alkene, alkyne groups or $(CH_2)_r$-3-14 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting N, O and S or substituted groups selected from alkyl;

n = 1-2; r = 0-6;

or X and Z may both represent (C_3-C_{13})carbocyclic residue or a 5-14 membered heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, and S, which may be substituted with substituted or unsubstituted groups selected from aryl heteroaryl, cycloalkyl, cycloalkene, alkene, alkyne or substituted alkyl groups;

Y represents $-(CR'R'')_p$, $-O(CR'R'')_p$, $-(CR'R'')_pO-$, $-C(O)(CR'R'')_p$, $-C(CR'R'')C(O)-$, $-C(O)O(CR'R'')_p$, $-OC(O)(CR'R'')_p$, $-C(CR'R'')C(O)O-$, $-C(CR'R'')OC(O)-$, $-NR'(CR'R'')_p-$, -NR'NR"-, $-(CR'R'')_pNR'-$, $-NR'C(O)(CR'R'')_p$, $CONR'(CR'R'')_p$, $-(CR'R'')_pNR'C(O)-$, $-(CR'R'')_pC(O)NR'-$, -NR'CONR'-, $-(CR'R'')_pS(O)_q-$, $-S(O)_q(CR'R'')_p-$, $-O(O)_qS(CR'R'')_p-$, $-(O)_qS(CR'R'')_pO-$, $-(O)_qSO(CR'R'')_p-$, $-NR'S(O)_q(CR'R'')_p-$, $-NR'S(O)_qNR'-$, $-OP(O)OR^a-$, $-P(O)OR^aO-$, $-NR'P(O)OR^a-$, $-P(O)OR^aNR'-$, $-(CR'R'')_pP(O)OR^a-$, $-P(O)OR^aC(R'R'')_p-$, $-(CR'R'')_pP(O)OR^aNR'-$, $-NR'P(O)OR^aC(R'R'')_p-$, $-S(O)_qNR'(CR'R'')_p-$, $-C(O)(CR'R'')NR'-$, $-NR'(CR,R'')_pC(O)-$, -CR'R"=CR'R", -C≡C-, =N-O-, -O-N=, wherein p = 0-2 and q = 0-2; R' and R" may be same or different and independently represent H, NH_2, OH, SH, halogen, CN, NO_2, alkyl group, linear or branched substituted or unsubstituted (C_1-C_6)alkyl, linear or branched substituted or unsubstituted (C_1-C_6)alkenyl, linear or branched substituted or unsubstituted (C_1-C_6)alkynyl groups;

R_4 represents H, -SR', halogen, -NR'R", OR', -CN, NO_2, $-(C_1-C_{10})$alkyl-R^a, $-(C_2-C_{10})$alkenyl-R^a, $-(C_2-C_{10})$alkynyl-R^a, $-(CR'R'')_p-R^a$, $-O(CR'R'')_pR^a-$, $-(CR'R'')_pO(CR'R'')_pR^a-$, $-(CR'R'')_pNR'(CR'R'')_pR^a-$, $-(CR'R'')_pC(O)(CR'R'')_pR^a-$, $-(CR'R'')_pOC(O)(CR'R'')_pR^a-$, $-(CR'R'')_pC(O)O(CR'R'')_pR^a-$, $-(CR'R'')_pNR'C(O)(CR'R'')_pR^a-$, $-(CR'R'')_pC(O)NR'(CR'R'')_pR^a-$, $-(CR'R'')_pS(O)_q(CR'R'')_pR^a-$, $-(CR'R'')_pS(O)_qNR'(CR'R'')_pR^a-$, $-(CR'R'')_pNR'S(O)_q(CR'R'')_pR^a-$, $-(CR'R'')_pOC(O)NR'(CR'R'')_pR^a-$, $-(CR'R'')_pNR'C(O)OCR'R'')_pR^a-$, wherein p = 0-2 and q = 0-2; R' and R" may be same or different and independently represent H, NH_2, SH, OH, halogen, CN, NO_2, alkyl group, linear or branched substituted or unsubstituted (C_1-C_6)alkyl, linear or branched substituted or unsubstituted (C_1-C_6)alkenyl, linear or branched substituted or unsubstituted (C_1-C_6)alkynyl groups, where R^a may represent H, halogen, alkyl group, linear or branched substituted or unsubstituted (C_1-C_6)alkyl, linear or branched substituted or unsubstituted (C_1-C_6)alkenyl, linear or branched substituted or unsubstituted (C_1-C_6)alkynyl groups, substituted or unsubstituted (C_3-C_{13}) carbocyclic residue or a substituted or unsubstituted 5-14 membered heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, and S;

With the proviso that when

i. 'A' represents $-C(=NOR_1)NHR_1$, X and Z may be same or different and represent (C_3-C_{13})carbocyclic residue or a 5-14 membered heterocyclic system containing 1-4 heteroatoms selected from the group consisting of N, O, and S, which may optionally be substituted;

ii. When Y represents =N-O-, -O-N=, X and Z may be same or different and represent (C_3-C_{13})carbocyclic residue or a 5-14 membered heterocyclic system containing 1-4

heteroatoms selected from the group consisting of N, O, and S, which may optionally be substituted;

iii. When Y represents $-O(O)_qS(CR'R'')_p$, $-(O)_qS(CR'R'')_pO-$, $-(O)_qSO(CR'R'')_p$, -NR'NR''-, $-OP(O)OR^a-$, $-P(O)OR^aO-$, -NR'P(O)OR^a, $-P(O)OR^aNR'-$, $-(CR'R'')_pP(O)OR^a-$, $-P(O)OR^aC(R'R'')_p-$, $-(CR'R'')_pP(O)OR^aNR'-$, $-NR'P(O)OR^aC(R'R'')_p-$, then X and Z may be same or different and represent substituted or unsubstituted (C_3-C_{13})carbocyclic residue;

The term "substituted" used alone or in combination with other radicals, denotes suitable substituents on that radical such as substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted aryl, etc, mentioned anywhere in the specification. The suitable substituents include, but are not limited to the following radicals, alone or in combination with other radicals, such as, hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heterocycloalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfonyloxy, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives, phosphonic acid and its derivatives.

The substituents on any of the substitutions, if substituted, may be selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, guanidino, hydrazino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino,

aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives, phosphonic acid and its derivatives

The various groups, radicals and substituents used anywhere in the specification are described in the following paragraphs.

The term "alkyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to twelve carbons, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, *iso*-hexyl, heptyl, octyl and the like.

The term "alkenyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing two to twelve carbons such as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term "alkenyl" includes dienes and trienes of straight and branched chains.

The term "alkynyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing two to twelve carbons, such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, and the like. The term "alkynyl" includes di- and tri-ynes.

The term "cycloalkyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term "cycloalkenyl" or used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropenyl, 1-cyclobutenyl, 2-cylobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, and the like.

The term "carbocycle" or "carbocyclic" used herein, either alone or in combination with other radicals, denotes any stable (C_3-C_7) membered monocyclic or bicyclic, or (C_7-C_{13}) membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles includes but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopropenyl, 1-cyclobutenyl, 2-cylobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, [3,3,0]bicyclooctayl, [4,3,0]bicyclononyl, [4,4,0]bicyclodecanyl,

[2,2,2]bicyclooctanyl, fluorenyl, phenyl, napthyl, indanyl, adamantyl, and tetrahydronaphthyl and the like.

The term "alkoxy" used herein, either alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached directly to an oxygen atom, such as methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like.

The term "alkenoxy" used herein, either alone or in combination with other radicals, denotes an alkenyl radical, as defined above, attached to an oxygen atom, such as vinyloxy, allyloxy, butenoxy, pentenoxy, hexenoxy, and the like.

The term "cycloalkoxy" used herein, either alone or in combination with other radicals, denotes a cycloalkyl radical as defined above, attached directly to an oxygen atom, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like.

The term "halo" or "halogen" used herein, either alone or in combination with other radicals, such as "haloalkyl", "perhaloalkyl" etc refers to a fluoro, chloro, bromo or iodo group. The term "haloalkyl" denotes a alkyl radical, as defined above, substituted with one or more halogens; such as perhaloalkyl, more preferably, perfluoro(C_1-C_6)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups. The term "haloalkoxy" denotes a haloalkyl, as defined above, directly attached to an oxygen atom, such as fluoromethoxy, chloromethoxy, fluoroethoxy chloroethoxy groups, and the like. The term "perhaloalkoxy" denotes a perhaloalkyl radical, as defined above, directly attached to an oxygen atom, trifluoromethoxy, trifluoroethoxy, and the like.

The term "aryl" or "aromatic" used herein, either alone or in combination with other radicals, denotes an aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused, such as phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and the like. The term 'aralkyl" denotes an alkyl group, as defined above, attached to an aryl, such as benzyl, phenethyl, naphthylmethyl, and the like. The term "aryloxy" denotes an aryl radical, as defined above, attached to an alkoxy group, such as phenoxy, naphthyloxy and the like, which may be substituted. The term "aralkoxy" denotes an arylalkyl moiety, as defined above, such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy, and the like, which may be substituted.

The term "heterocyclyl" or "heterocyclic" used herein, either alone or in combination with other radicals, denotes saturated, partially saturated and unsaturated ring-shaped radicals, the heteroatoms selected from nitrogen, sulfur and oxygen. Examples of

saturated heterocyclic radicals include aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl, and the like; examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, and the like.

The term "heteroaryl" or "heteroaromatic" used herein, either alone or in combination with other radicals, denotes unsaturated 5 to 6 membered heterocyclic radicals containing one or more hetero atoms selected from O, N or S, such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzothienyl, indolinyl, indolyl, azaindolyl, azaindolinyl, benzodihydrofuranyl, benzodihydrothienyl, pyrazolopyrimidinyl, pyrazolopyrimidonyl, azaquinazolinyl, azaquinazolinoyl, pyridofuranyl, pyridothienyl, thienopyrimidyl, thienopyrimidonyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, quinazolonyl, pyrimidonyl, pyridazinyl, triazinyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl, and the like.

.The term "heterocyclylalkyl" used herein, either alone or in combination with other radicals, represents a heterocyclyl group, as defined above, substituted with an alkyl group of one to twelve carbons, such as pyrrolidinealkyl, piperidinealkyl, morpholinealkyl, thiomorpholinealkyl, oxazolinealkyl, and the like, which may be substituted. The term "heteroaralkyl" used herein, either alone or in combination with other radicals, denotes a heteroaryl group, as defined above, attached to a straight or branched saturated carbon chain containing 1 to 6 carbons, such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like. The terms "heteroaryloxy", "heteroaralkoxy", "heterocycloxy", "heterocylylalkoxy" denotes heteroaryl, heteroarylalkyl, heterocyclyl, heterocylylalkyl groups respectively, as defined above, attached to an oxygen atom.

The term "acyl" used herein, either alone or in combination with other radicals, denotes a radical containing one to eight carbons such as formyl, acetyl, propanoyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, which may be substituted.

The term "acyloxy" used herein, either alone or in combination with other radicals, denotes a radical acyl, as defined above, directly attached to an oxygen atom, such as acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like.

The term "acylamino" used herein, either alone or in combination with other radicals, denotes an acyl group as defined earlier, may be CH_3CONH, C_2H_5CONH, C_3H_7CONH, C_4H_9CONH, C_6H_5CONH and the like, which may be substituted.

The term "mono-substituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with one group selected from $(C_1\text{-}C_6)$alkyl, substituted alkyl, aryl, substituted aryl or arlylalkyl groups. Examples of monoalkylamino group include methylamine, ethylamine, *n*-propylamine, *n*-butylamine, *n*-pentylamine and the like.

The term 'disubstituted amino" used herein, either alone or in combination with other radicals, denotes an amino group, substituted with two radicals that may be same or different selected from $(C_1\text{-}C_6)$alkyl, substituted alkyl, aryl, substituted aryl, or arylalkyl groups, such as dimethylamino, methylethylamino, diethylamino, phenylmethyl amino and the like.

The term "arylamino" used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through amino having a free valence bond from the nitrogen atom, such as phenylamino, naphthylamino, N-methyl anilino and the like.

The term "aralkylamino" used herein, either alone or in combination with other radicals, denotes an arylalkyl group as defined above linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-napthylmethylamino, 2-(1-napthyl)ethylamino and the like.

The term "oxo" or "carbonyl" used herein, either alone (-C=O-) or in combination with other radicals, such as "alkylcarbonyl", denotes a carbonyl radical (–C=O-) substituted with an alkyl radical such as acyl or alkanoyl, as described above.

The term "carboxylic acid" used herein, alone or in combination with other radicals, denotes a –COOH group, and includes derivatives of carboxylic acid such as esters and amides. The term "ester" used herein, alone or in combination with other radicals, denotes –COO- group, and includes carboxylic acid derivatives, where the ester moieties are alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, and the like, which may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, napthyloxycarbonyl, and the like, which may be substituted; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, napthylmethoxycarbonyl, and the like, which may be substituted; heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group, is as defined above, which may be

substituted; heterocyclyloxycarbonyl, where the heterocyclic group, as defined earlier, which may be substituted.

The term "amide" used herein, alone or in combination with other radicals, represents an aminocarbonyl radical (H_2N-C=O-), wherein the amino group is mono- or di-substituted or unsubstituted, such as methylamide, dimethylamide, ethylamide, diethylamide, and the like. The term "aminocarbonyl" used herein, either alone or in combination with other radicals, with other terms such as 'aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl", and "N-alkyl-N-hydroxyaminocarbonylalkyl", substituted or unsubstituted. The terms "N-alkylaminocabonyl" and "N,N-dialkylaminocarbonyl" denotes aminocarbonyl radicals, as defined above, which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote amiocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl, and one aryl radical. The term "aminocarbonylalkyl" includes alkyl radicals substituted with aminocarbonyl radicals.

The term "hydroxyalkyl" used herein, either alone or in combination with other radicals, denotes an alkyl group, as defined above, substituted with one or more hydroxy radicals, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like.

The term "aminoalkyl" used herein, alone or in combination with other radicals, denotes an amino ($-NH_2$) moiety attached to an alkyl radical, as defined above, which may be substituted, such as mono- and di-substituted aminoalkyl. The term "alkylamino" used herein, alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached to an amino group, which may be substituted, such as mono- and di-substituted alkylamino.

The term "alkoxyalkyl" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an alkyl group, such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like. The term "aryloxyalkyl" used herein, alone or in combination with other radicals, includes phenoxymethyl, napthyloxymethyl, and the like. The term "aralkoxyalkyl" used herein, alone or in combination with other radicals, includes $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$, and the like.

The term "alkylthio" used herein, either alone or in combination with other radicals, denotes a straight or branched or cyclic monovalent substituent comprising an alkyl group of one to twelve carbon atoms, as defined above, linked through a divalent sulfur atom having a free

valence bond from the sulfur atom, such as methylthio, ethylthio, propylthio, butylthio, pentylthio and the like. Examples of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like, which may be substituted.

The term "thioalkyl" used herein, either alone or in combination with other radicals, denotes an alkyl group, as defined above, attached to a group of formula –SR', where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be substituted.

The term "arylthio' used herein, either alone or in combination with other radicals, denotes an aryl group, as defined above, linked through a divalent sulfur atom, having a free valence bond from the sulfur atom such as phenylthio, napthylthio and the like.

The term "alkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an alkoxycarbonyl group, as defined above, attached to an amino group, such as methoxycarbonylamino, ethoxycarbonylamino, and the like. The term "aryloxycarbonylamino" used herein, alone or in combination with other radicals, denotes an aryloxycarbonyl group, as defined above, attached to the an amino group, such as C_6H_5OCONH, $C_6H_5OCONCH_3$, $C_6H_5OCONC_2H_5$, $C_6H_4(CH_3O)CONH$, $C_6H_4(OCH_3)OCONH$, and the like. The term "aralkoxycarbonylamino" used herein, alone or in combination with other radicals, denotes an aralkoxycarbonyl group, as defined above, attached to an amino group $C_6H_5CH_2OCONH$, $C_6H_5CH_2CH_2CH_2OCONH$, $C_6H_5CH_2OCONHCH_3$, $C_6H_5CH_2OCONC_2H_5$, $C_6H_4(CH_3)CH_2OCONH$, $C_6H_4(OCH_3)CH_2OCONH$, and the like.

The term "aminocarbonylamino", "alkylaminocarbonylamino", "dialkylaminocarbonylamino" used herein, alone or in combination with other radicals, denotes a carbonylamino (-$CONH_2$) group, attached to amino(NH_2), alkylamino group or dialkylamino group respectively, where alkyl group is as defined above.

The term "amidino" used herein, either alone or in combination with other radicals, denotes a –C(=NH)-NH_2 radical. The term "alkylamidino" denotes an alkyl radical, as discussed above, attached to an amidino group.

The tem "hydrazino" used herein, either alone or in combination with other radicals, denotes –NHNH-, suitably substituted with other radicals, such as alkyl hydrazino, where an alkyl group, as defined above is attached to a hydrazino group.

The term "alkoxyamino" used herein, alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an amino group. The term "hydroxyamino" used herein, alone or in combination with other radicals, denotes –NHOH moiety, and may be substituted.

The term "sulfenyl" or "sulfenyl and its derivatives" used herein, alone or in combination with other radicals, denotes a bivalent group, –SO- or R_xSO, where R_x is substituted or unsubstituted alkyl, aryl, heteroaryl, heterocyclyl, and the like.

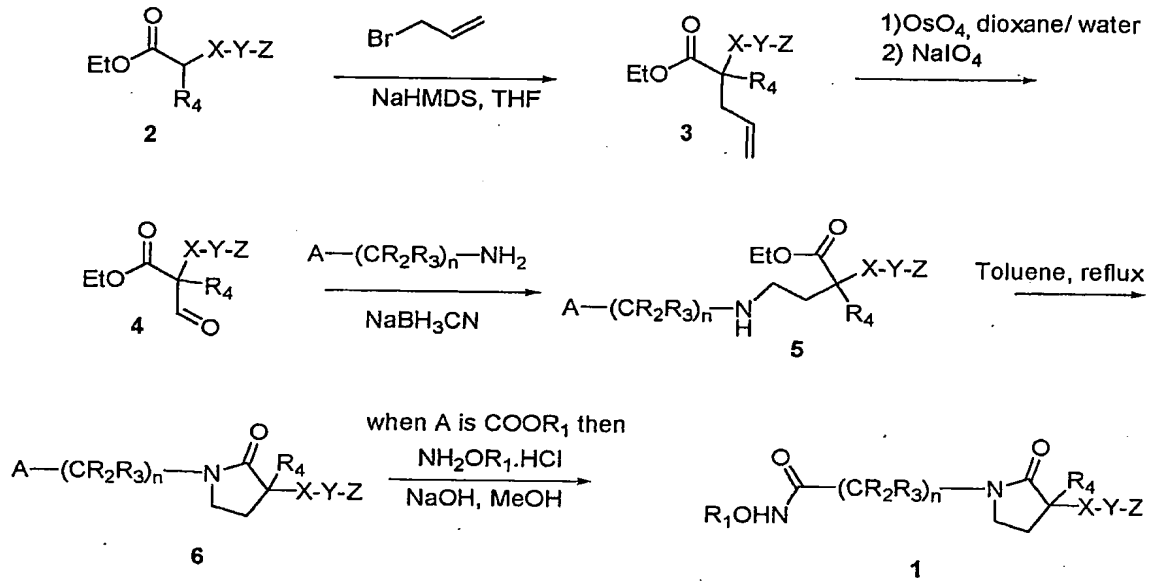
The term "sulfonyl" or "sulfones and its derivatives" used herein, either alone or in combination with other radicals, with other terms such as alkylsulfonyl, denotes divalent radical – SO_2-, or R_xSO_2-, where R_x is substituted or unsubstituted groups selected from alkyl, aryl, heteroaryl, heterocyclyl, and the like. "Alkylsulfonyl" denotes alkyl radicals, as defined above, attached to a sulfonyl radical, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like. The term "arylsulfonyl" used herein, either alone or in combination with other radicals, denotes aryl radicals, as defined above, attached to a sulfonyl radical, such as phenylsulfonyl and the like.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

Several synthesis routes can be employed to prepare the compounds of the present invention well known to one skilled in the art of organic synthesis. The compounds of formula (I) can be synthesized using the methods described below, together with conventional techniques known to those skilled in the art of organic synthesis, or variations thereon as appreciated by those skilled in the art. Referred methods include, but not limited to those described below.

When preparing or elaborating compounds of the invention containing heterocyclic rings, those skilled in the art recognize that substituents on the ring may be prepared before, after or concomitant with the construction of the pyrrolidinone ring. It is understood by those skilled in the art that the nature and order of the synthetic steps presented may be varied for the purpose of optimizing the formation of the compounds of the present invention. Those skilled in the art will recognize that certain reactions are carried out when other potentially reactive functionality on the molecule is masked or protected to avoid undesired side reactions and/or increasing the yield of the reaction. The desired protective groups may be found T. W. Greene, P.G.M. Wuts " Protective Groups in Organic Synthesis" 2nd edition 1991, Wiley and Sons, New York. It is understood by one skilled in the art of organic synthesis that the protective groups present on various reactive functionality of the molecule must be compatible with reagents and reactions proposed and it will be readily apparent to one skilled in the art an alternate methods must be used. The reactions are performed in solvents appropriate to the reagents and materials used and are suitable for the transformations being effected. The pyrrolidinone compounds of the present invention are prepared by methods outlined in scheme 1.

SCHEME-1



The compounds of the present invention may be prepared by treating suitably substituted ester compound of formula (2) where X, Y, Z and R_4 are defined as earlier, with allyl bromide under basic condition using bases such as sodium bis(trimethylsilyl)amide, lithium N,N-diisopropylamide, potassium hydride, sodium hydride and the like or mixtures thereof, to give unsaturated ester (3) where all the symbols are as defined earlier. The double bond is then oxidized to give aldehyde (4) where all the symbols are as defined earlier by ozonolysis or by dihydroxylation with OsO_4 followed by diol cleavage using $NaIO_4$. Treatment of (4) with chiral amino acid under reductive amination condition to get amine derivative (5) where all the symbols are as defined earlier. Reductive amination can be carried out with different reducing reagents like $NaCNBH_3$, $NaB(OAc)_3H$, $NaBH_4$ and like. Lactamization of (5) may be carried out by thermally induced method to get (6) where all the symbols are as defined earlier. Compound (6) is the mixture of two diastereomers epimeric at the quaternary center. Diastereomers of (6) are either separated or taken as such to the next step. When compound (6) is ester, it is converted to hydroxamic acid of formula (I) where all the symbols are as defined earlier by treatment with hydroxylamine under basic condition (KOH, NaOH) in alcoholic solvent such as MeOH, EtOH

and the like or mixtures thereof; while keeping the temperature of the reaction in the range of –20 ^{0}C to 50 ^{0}C.

The compounds of the present invention have asymmetric centers and occur either as racemates or racemic mixtures as well as individual diastereomers of any of the possible isomers, including optical isomers, being included in the present invention These can be isolated using conventional techniques known to persons skilled in the art (Jaques et al. "Enantiomers, Racemates and Resolution", Wiley Interscience, 1981; R. A. Sheldon, in "Chirotechnology", Marcel Dekker, Inc. NY, Basel, 1993, 173-204 and references therein; A. N. Collins, G. N. Sheldrack and J Crosby, in "Chirality in Industry II", John Wiley & Sons, Inc, 1997, 81-98 and references therein; E. L. Eliel and S. H. Wilen, in "Stereochemistry of Organic Compound", John Wiley & Sons, Inc, 1999, 297-464 and references therein.).

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of compound (I) which is sufficiently basic, for example an acid addition salt with an inorganic or organic acid such as hydrochloric acid, hydrobromic, sulfuric, trifluoroacetic, citric or maleic acid and the like; or, for example a salt of compound (I) which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or a magnesium salt, or an ammonium salt; or a salt of an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine and the like.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium *tert*-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride, magnesium alkoxide and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, *tert*-butanol, 2-butanone, dioxane, propanol, butanol, isopropanol, di*iso*propyl ether, *tert*-butyl ether or mixtures thereof may be used. Organic bases such as lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine, tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, wherever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, malic acid, lactic acid, maleic acid, salicylic acid, citric acid, ascorbic acid, benzene sulfonic acid, *p*-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, THF, acetonitrile, DMF or a lower alkyl ketone such as acetone, or mixtures thereof.

Another aspect of the present invention comprises a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers diluents and the like.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in "Remington: the Science and Practice of Pharmacy", 19th Ed., 1995. The compositions may be in the conventional forms, such as capsules, tablets, powders, solutions, suspensions, syrups, aerosols or topical applications. They may contain suitable solid or liquid carriers or in suitable sterile media to form injectable solutions or suspensions. The compositions may contain 0.5 to 20 %, preferably 0.5 to 10 % by weight of the active compound, the remaining being pharmaceutically acceptable carriers, excipients, diluents, solvents and the like.

Typical compositions containing a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipients which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material, which acts as a vehicle, excipients or medium for the active compound. The active compound can be absorbed on a granular solid container for example in a sachet. Some of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium sterate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acids monoglycerides and diglycerides, pentaerythritol fatty acids esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preservatives, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active drug to the appropriate or desired site of action effectively, such as oral, nasal, transdermal, pulmonary or parental e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, preferably through oral route.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula (I) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agent, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabens.

For parental application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablet, dragees or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferably, carriers for tablets, dragees or capsules include lactose, corn starch and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

The effective amount of the drug will depend on the relative efficacy of the compounds of the present invention, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. Suitably, a unit dosage form of a composition of the invention may contain from 0.1 to 1000 mg of a compound of the invention (0.001 to 10 mg via inhalation) and more usually from 1 to 500 mg. Such compositions may be administered from 1 to 6 times a day, more usually from 2 to 4 times a day, in a manner such that the daily dose is from 1 mg to 1 g for a 70-kg human adult and more particularly from 5 to 500 mg. That is in the range of about 1.4 x 10^{-2} mg/kg/day to 14 mg/kg/day and more particularly in the range of 5 x 10^{-2} mg/kg/day to 7 mg/kg/day.

In another aspect of the present invention, method of treatment and/or prevention of the diseases mentioned above are provided.

In a further aspect of the present invention, use of one or more compounds of the general formula (I) or pharmaceutically acceptable salts, for the preparation of a medicament thereof for the treatment and/or prevention of diseases mentioned in this document is provided.

Dated this 7th day of January 2004

Signature _____
(Dr. B. B. Lohray, President, Zydus Research Centre)
for **Cadila Healthcare Ltd.**

To
The Controller of Patents
The Patent Office,
at_____

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
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New Delhi 110 048
INDE

Date of mailing *(day/month/year)* 07 July 2005 (07.07.2005)	
Applicant's or agent's file reference ZRC-MC-020	**IMPORTANT NOTIFICATION**
International application No. PCT/IN2005/000010	International filing date *(day/month/year)* 07 January 2005 (07.01.2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 09 January 2004 (09.01.2004)
Applicant CADILA HEALTHCARE LIMITED et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
09 January 2004 (09.01.2004)	22/MUM/2004	IN	19 May 2005 (19.05.2005)

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